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| APPLICATION NO.                   | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|-----------------------------------|-------------|----------------------|---------------------|------------------|
| 10/559,783                        | 12/08/2005  | Mitsuko Kosaka       | 64614(70904)        | 1080             |
| 21874                             | 7590        | 08/23/2007           |                     |                  |
| EDWARDS ANGELL PALMER & DODGE LLP |             |                      | EXAMINER            |                  |
| P.O. BOX 55874                    |             |                      | DUTT, ADITI         |                  |
| BOSTON, MA 02205                  |             |                      | ART UNIT            | PAPER NUMBER     |
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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

|                              |                                      |  |  |
|------------------------------|--------------------------------------|--|--|
| <b>Office Action Summary</b> | <b>Application No.</b><br>10/559,783 | <b>Applicant(s)</b><br>KOSAKA, MITSUKO |  |
|                              | <b>Examiner</b><br>Aditi Dutt        | <b>Art Unit</b><br>1649                |  |

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

### Status

- 1) ☒ Responsive to communication(s) filed on 12 June 2007.
- 2a) ☒ This action is **FINAL**.                      2b) ☐ This action is non-final.
- 3) ☒ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

### Disposition of Claims

- 4) ☒ Claim(s) 1-6 and 8-16 is/are pending in the application.
- 4a) Of the above claim(s) 12-14 is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1-6, 8-11, 15-16 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

### Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

### Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All    b) ☐ Some \*    c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

### Attachment(s)

- |  |   |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892)                     | 4) <input type="checkbox"/> Interview Summary (PTO-413)           |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____                                      |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)          | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date _____  | 6) <input type="checkbox"/> Other: _____                          |

## **DETAILED ACTION**

### ***Status of Claims***

1. The amendments filed on 12 June 2007 have been entered into the record and have been fully considered. Claims 1, 6, and 8 are amended. Claim 7 is canceled. Claims 12-14 have been "withdrawn" by Applicant. New claims 15-16 are added.
2. Claims 1-6, 8-11, and 15-16, drawn to a method for producing tissue cells culturing iris pigment epithelial cells and obtaining pluripotent cells therefrom, are under consideration in the instant application.
3. Any objection or rejection of record, which is not expressly repeated in this action has been overcome by Applicants response and withdrawn.
4. Applicant's arguments filed on 12 June 2007, have been fully considered. New grounds of objection and rejection are as follow.

### ***Response to Amendment***

#### **Withdrawn objections and/or rejections**

5. Upon consideration of the Applicant's amendment, all claim objections and rejections, not reiterated herein have been withdrawn, as overcome by cancellation and/or amendment of claims (12 June 2007).
6. Rejection of claims 1-11, under 35 U.S.C. 112, second paragraph is withdrawn, because of appropriate amendment and clarification of the claims.

Applicant's note pointing out the error that claim 5 does not recite "tissue-restoring" is acknowledged. Examiner apologizes for the typo.

7. Rejection of claims 1-11, under 35 U.S.C. 112, first paragraph, scope of enablement is withdrawn, because of amendment of the claims, and Applicant's arguments that were found to be persuasive.

Claim rejections/objections maintained/new grounds of rejection

35 U.S.C. 112-first paragraph- Written Description

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. The rejections of claims 1-11, are applied to the amended claims 1-6, 8-11 and 16, for reasons of record in the Office Action dated 13 March 2007.
9. The claims are drawn to a method for producing tissue cells comprising: (i) obtaining iris pigment epithelial cells from an eyeball of a postnatal animal, for example, chicken, mouse, rat or human, by enzyme treatment (claims 1-3, 5-6); (ii) culturing epithelial cells by floated coagulated mass culturing technique to obtain pluripotent stem cells, that are Oct-3/4 positive, and/or tridermic differentiable (claims 1, 4). The claims further teach that the differentiation inducing conditions comprise, culture of the cells in the presence of serum (fetal calf or avian) with a growth factor (FGF or EGF) (claims 7-11). The claims further recite the method for the generation of an embryoid body (claim 16).

10. Applicant asserts that the specification discloses Applicant's ability "to detect markers of all three germ layers" from iris pigment epithelial cells (IPE) in culture, by the formation of an "embryoid body". Applicant further demonstrates the formation of cardiac myocytes and accordingly adds claim 15 with the limitation reciting the formation of myocardial cells. In view of these arguments, Applicant requests the withdrawal of the rejection.

11. Applicant's arguments directed to the claimed invention have been fully considered but have not been found to be persuasive. Although Applicant describes the markers for the three germ layers, Applicant does not provide working examples to demonstrate the differentiation of IPE cells, to cells and tissues characterized by all three germ layers. As stated in the previous Office Action (page 9, para 21; page 10, para 23, para 25), it is reiterated as follows:

The brief description in the specification of one example of mesodermal cells (cardiac myocytes), one example of ectodermal cells (iris), does not provide adequate written description of an entire genus of tissues and cells that are tridermic differentiable. To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of specific physiological characteristics, physical and/or chemical properties, functional features, structure/function correlation, or any combination thereof. However, in this case, the specification has not shown a relationship between the claimed genus of tridermic differentiable stem cells, derived from the iris pigment epithelial cells.

The skilled artisan cannot envision the entire genus of tridermic differentiable stem cells, of the encompassed methods, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method.

Therefore, only methods of generation of cardiac myocytes and iris, but not the full breadth of the claim meets the written description provision of 35 U.S.C. §112, first paragraph.

Thus claims 1-6, 8-11 and 16 stand rejected.

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

12. The rejection of claims 1-11, under 35 U.S.C. 103(a) as being unpatentable over Kosaka et al. (Exp Cell Res 245: 245-251, 1998), and Haruta et al., (Nat Neurosc 4: 1163-1164, 2001); in view of Reynolds and Weiss (Sc. 255: 1707-1710, 1992), are applied to the amended claims 1-6, 8-11 and 15, for reasons of record in the Office Action, dated 13 March 2007.
13. Applicant argues that the floated coagulated mass culturing technique of Reynolds et al. fails to teach that it can be used for any cell type other than neural cells. For example, Reynolds et al do not indicate that the floated coagulated mass culture method could be applicable to IPE cells of the instant invention. Furthermore, Applicant argues that using Reynolds conditions, one would not expect an IPE cell to behave like a neural stem cell in vitro, or would form a neurosphere like that of Reynolds. Hence Applicant alleges that the references fail to provide any motivation to combine the teachings of the prior art

for making an obviousness rejection of the claimed invention. Applicant finally concludes by stating that this was an unexpected discovery.

14. Applicant's arguments have been fully considered but have not been found to be persuasive. Reynolds et al teach a cell culture method suggestive of the floated coagulated mass culturing technique using neurospheres. Although Reynolds et al. teach the differentiation of the neurosphere to neural and neuroepithelial stem cells, the reference essentially teaches a technique for selective culturing and differentiation to various cell types, which can be broadly applied to various cells and tissues. Using cell-specific markers, one can further detect the different cells generated by the differentiation process. Additionally, the use of the neurosphere technique for selective culturing of the IPE cells was inherent in the instant specification (page 19, para 2).
15. Applicant argues that Reynolds et al. do not teach IPE cell types and thus the neurosphere method cannot be a motivation for using for IPE cells. However, neural, neuroepithelial and IPE cells are all ectodermal cells, and absent evidence to the contrary, the technique of using neurospheres for IPE cell differentiation in culture, would be obvious to one skilled in the art in view of Reynolds et al. Furthermore, in considering the disclosure of a reference, it is proper to take into account not only specific teaching of the reference but also the inferences which one skilled in the art would be reasonably be expected to draw therefrom (*In re Preda*, 401 F.2d 825, 159 USPQ 342, 344 (CCPA 1968)). Also, a reference must be considered, under 35 U.S.C. 103, not only for what it

expressly teaches but also for what it fairly suggests; all disclosures of prior art, including unpreferred embodiments, must be considered in determining obviousness (*In re Burckel* 201 USPQ 67 (CCPA 1979)).

16. Furthermore, although the references (Kosaka et al and Haruta et al) do not explicitly teach the differentiation to myocardial cells, this limitation will be an inherent feature, since the combined references teach the culture limitations of the instant application. Additionally, since the cells of Kosaka et al. and Haruta et al are derived from the same source as the instant application, the three inherently display the same differentiation properties and express similar marker, absent evidence to the contrary. That the references are silent on the expression of the cardiac marker does not provide proof of the cell being different, particularly if the other conditions (as stated above) are satisfied.

17. As stated in the previous Office Action (page 13, para 36):

It would have been, therefore, obvious to the person of ordinary skill in the art at the time the claimed invention was made to modify the method of culturing the iris pigment epithelial cells of Kosaka et al. and Haruta et al., to the floated coagulated mass culture technique as taught by Reynolds and Weiss. The person of ordinary skill in the art would have been motivated to use this technique for cell culture and differentiation as this would facilitate the selection of a specific cell type aggregate by antibody immuno-staining (Reynolds and Weiss, page 708, Figure 1E and 1F). The person of ordinary skill in the art would have expected success because the method of floated coagulated mass technique (or neurosphere), was well established and accepted in the art at the time the invention was made.

18. As stated in the previous Office Action, the claimed invention stays *prima facie* obvious over the combined teachings of Kosaka et al., Haruta et al. and Reynolds and Weiss. Thus the rejection is maintained.



***Conclusion***

19. No claims are allowed.
20. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).
21. A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than **SIX MONTHS** from the date of this final action.
22. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Aditi Dutt whose telephone number is (571) 272-9037. The examiner can normally be reached on Monday through Friday, 9:00 a.m. to 5:00 p.m.
23. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan, can be reached on **(571) 272-0841**. The

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fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

24. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov/>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

AD  
15 August 2007

**/Gary B. Nickol/**  
**Supervisory Patent Examiner, Art Unit 1646**